

AMENDMENTS TO THE CLAIMS

1. (Original) A pharmaceutical composition comprising a beta-blocker and an adenosine A₁ receptor antagonist (AA₁RA).

2. (Original) The composition of Claim 1, wherein said beta-blocker is selected from the group consisting of acebutolol hydrochloride, atenolol, betaxolol hydrochloride, bisoprolol fumarate, carteolol hydrochloride, esmolol hydrochloride, metoprolol, metoprolol tartrate, nadolol, penbutolol sulfate, pindolol, propranolol hydrochloride, succinate, and timolol maleate, or a pharmaceutically acceptable salt, prodrug, ester, or amide thereof.

3. (Original) A pharmaceutical composition comprising an angiotensin converting enzyme (ACE) inhibitor and an adenosine A₁ receptor antagonist (AA₁RA).

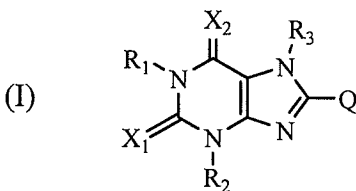
4. (Original) A pharmaceutical composition comprising an angiotensin II receptor blocker (ARB) and an adenosine A₁ receptor antagonist (AA₁RA).

5. (Original) A pharmaceutical composition comprising an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor blocker (ARB), and an adenosine A₁ receptor antagonist (AA₁RA).

6. (Original) The composition of Claim 3, wherein said ACE inhibitor is selected from the group consisting of lisinopril, enalapril, quinapril, ramipril, benazepril, captopril, fosinopril, moexipril, trandolapril, and perindopril, or a pharmaceutically acceptable salt, prodrug, ester, or amide thereof.

7. (Original) The composition of Claims 4, wherein said ARB is selected from the group consisting of losartan, irbesartan, candesartan, telmisartan, eposartan, and valsartan.

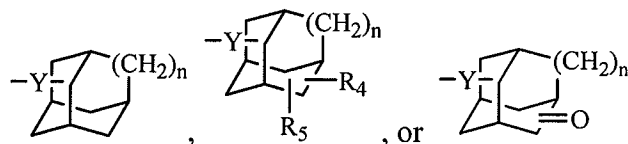
8. (Previously presented) The composition of any one of Claims 1, 3, or 4, wherein said AA₁RA is a xanthine-derivative compound of Formula I or a pharmaceutically acceptable salt thereof,



wherein

each of X₁ and X₂ independently represents oxygen or sulfur;

Q represents:

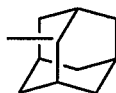


where Y represents a single bond or alkylene having 1 to 4 carbon atoms, n represents 0 or 1;

each of R₁ and R₂ independently represents hydrogen, lower alkyl, allyl, propargyl, or hydroxy-substituted, oxo-substituted or unsubstituted lower alkyl, and R₃ represents hydrogen or lower alkyl, or

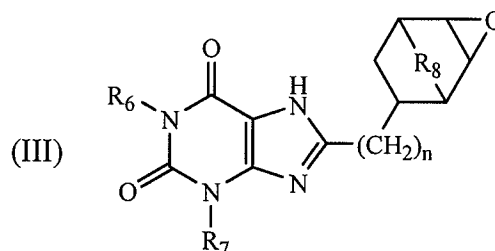
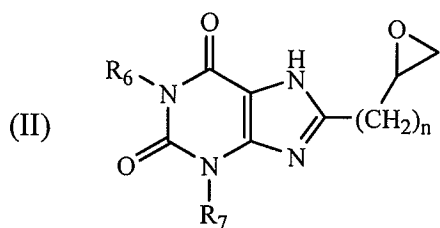
R₄ and R₅ are the same or different and each represent hydrogen or hydroxy, and when both R₄ and R₅ are hydrogen, at least one of R₁ and R₂ is hydroxy-substituted or oxo-substituted lower alkyl,

provided that when Q is



then R₁, R₂ and R₃ are not simultaneously methyl,

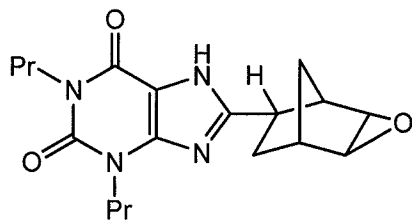
or wherein said AA₁RA is a xanthine epoxide-derivative compound of Formula II or Formula III, or a pharmaceutically acceptable salt thereof,



wherein R₆ and R₇ are the same or different, and can be hydrogen or an alkyl group of 1-4 carbons, R₈ is either oxygen or (CH₂)₁₋₄, and n=0-4.

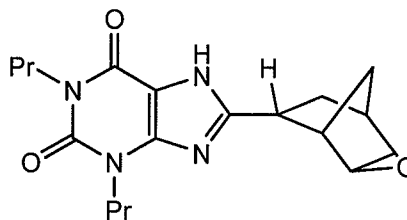
9. (Original) The composition of Claim 8, wherein said AA₁RA is selected from the group consisting of 8-(noradamantan-3-yl)-1,3-dipropylxanthine; 1,3-Diallyl-8-(3-noradamantyl)xanthine, 3-allyl-8-(3-noradamantyl)-1-propargylxanthine, 8-(trans-9-hydroxy-3-tricyclo[3.3.1.0^{3,7}]nonyl)-1,3-dipropylxanthine, 8-(cis-9-hydroxy-3-tricyclo[3.3.1.0^{3,7}]nonyl)-1,3-dipropylxanthine, 8-(trans-9-hydroxy-3-tricyclo[3.3.1.0^{3,7}]nonyl)-1-(2-oxopropyl)-3-

propylxanthine, 1-(2-hydroxypropyl)-8-(trans-9-hydroxy-3-tricyclo[3.3.1.0^{3,7}]nonyl)-3-



propylxanthine,

, and



or a pharmaceutically acceptable salt thereof.

10. (Original) A method of treating cardiovascular disease comprising identifying a patient in need of such treatment, and administering a pharmaceutical composition of Claim 1 to said patient.

11. (Original) The method of Claim 10, wherein said cardiovascular disease is congestive heart failure, hypertension, asymptomatic left ventricular dysfunction, or coronary artery disease.

12. (Original) The method of Claim 10, wherein said patient is in need of after-load reduction.

13. (Original) The method of Claim 10, wherein said patient requires additional diuretic therapy or is refractory to diuretic therapy.

14. (Original) A method of treating cardiovascular disease or renal disease comprising identifying a patient in need of such treatment, and administering a pharmaceutical composition of any one of Claims 3-5 to said patient.

15. (Original) The method of Claim 14, wherein said patient suffers from cardiovascular disease selected from congestive heart failure, hypertension, asymptomatic left ventricular dysfunction, or acute myocardial infarction, or wherein said patient is in need of after-load reduction, or wherein said patient is refractory to diuretic therapy.

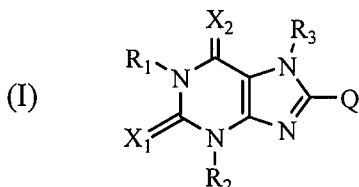
16. (Original) The method of Claim 14, wherein said renal disease is renal hypertrophy, renal hyperplasia, microproteinuria, proteinuria, diabetic nephropathy, contrast-mediated nephropathy, toxin-induced renal injury, or oxygen free-radical mediated nephropathy.

17. (Original) A method of treating alkalosis comprising identifying a patient in need thereof and administering an adenosine A₁ receptor antagonist (AA₁RA) to said patient.

18. (Original) The method of Claim 17, wherein said alkalosis is metabolic alkalosis or respiratory alkalosis.

19. (Original) The method of Claim 17, wherein said patient has edema, is on diuretic therapy, or suffers from acid loss through the patient's upper gastrointestinal tract.

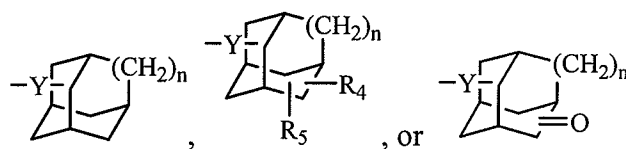
20. (Previously presented) The method of Claim 17, wherein said AA₁RA is a xanthine-derivative compound of Formula I or a pharmaceutically acceptable salt thereof,



wherein

each of X₁ and X₂ independently represents oxygen or sulfur;

Q represents:

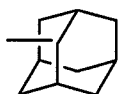


where Y represents a single bond or alkylene having 1 to 4 carbon atoms, n represents 0 or 1;

each of R₁ and R₂ independently represents hydrogen, lower alkyl, allyl, propargyl, or hydroxy-substituted, oxo-substituted or unsubstituted lower alkyl, and R₃ represents hydrogen or lower alkyl, or

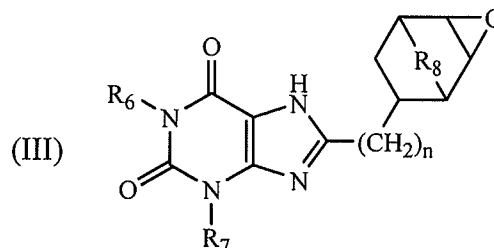
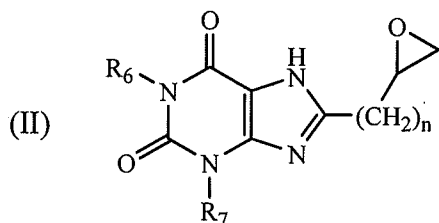
R₄ and R₅ are the same or different and each represent hydrogen or hydroxy, and when both R₄ and R₅ are hydrogen, at least one of R₁ and R₂ is hydroxy-substituted or oxo-substituted lower alkyl,

provided that when Q is



then R₁, R₂ and R₃ are not simultaneously methyl,

or wherein said AA₁RA is a xanthine epoxide-derivative compound of Formula II or Formula III, or a pharmaceutically acceptable salt thereof,

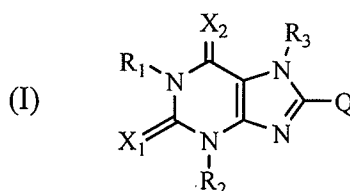


wherein R_6 and R_7 are the same or different, and can be hydrogen or an alkyl group of 1-4 carbons, R_8 is either oxygen or $(CH_2)_{1-4}$, and $n=0-4$.

21. (Original) A method of treating diabetic nephropathy comprising identifying a patient in need thereof and administering an adenosine A_1 receptor antagonist (AA_1RA) to said patient.

22. (Original) The method of Claim 21, wherein said patient is pre-diabetic or is in early stage diabetes.

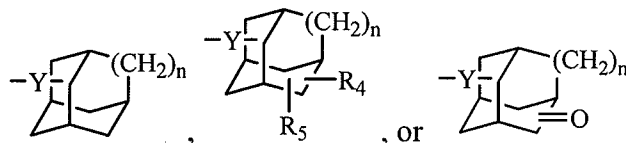
23. (Previously presented) The method of Claim 21, wherein said AA_1RA is a xanthine-derivative compound of Formula I or a pharmaceutically acceptable salt thereof,



wherein

each of X_1 and X_2 independently represents oxygen or sulfur;

Q represents:

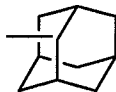


where Y represents a single bond or alkylene having 1 to 4 carbon atoms, n represents 0 or 1;

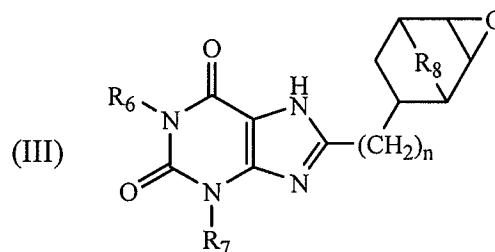
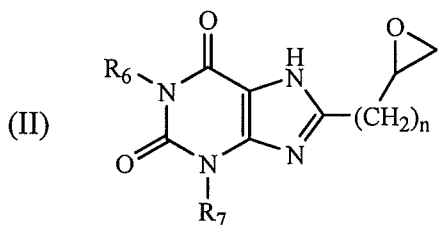
each of R_1 and R_2 independently represents hydrogen, lower alkyl, allyl, propargyl, or hydroxy-substituted, oxo-substituted or unsubstituted lower alkyl, and R_3 represents hydrogen or lower alkyl, or

R_4 and R_5 are the same or different and each represent hydrogen or hydroxy, and when both R_4 and R_5 are hydrogen, at least one of R_1 and R_2 is hydroxy-substituted or oxo-substituted lower alkyl,

provided that when Q is



then R_1 , R_2 and R_3 are not simultaneously methyl,
or wherein said AA₁RA is a xanthine epoxide-derivative compound of Formula II or Formula III,
or a pharmaceutically acceptable salt thereof,



wherein R_6 and R_7 are the same or different, and can be hydrogen or an alkyl group of 1-4 carbons, R_8 is either oxygen or $(CH_2)_{1-4}$, and $n=0-4$.

24. (Original) The method of Claim 21, further comprising administering a compound selected from the group consisting of a protein kinase C inhibitor, an inhibitor of tissue proliferation, an antioxidant, an inhibitor of glycosylation, and an endothelin B receptor inhibitor.

25. (Original) The method of Claim 21, wherein said treating comprises preventing, reversing, or ameliorating a disease selected from the group consisting of renal hypertrophy, renal hyperplasia, microproteinuria, and proteinuria.

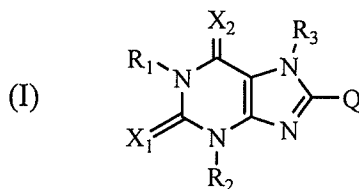
26. (New) A method of treating cardiovascular disease in a patient, comprising:
identifying a patient in need of treatment for cardiovascular disease; and
administering an adenosine A₁ receptor antagonist in conjunction with a beta blocker to said patient.

27. (New) The method of Claim 26, wherein said cardiovascular disease is congestive heart failure, hypertension, asymptomatic left ventricular dysfunction, or coronary artery disease.

28. (New) The method of Claim 26, wherein said patient is in need of after-load reduction.

29. (New) The method of Claim 26, wherein said patient requires additional diuretic therapy or is refractory to diuretic therapy.

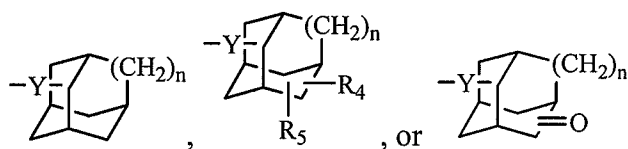
30. (New) The method of Claim 26, wherein said AA₁RA is a xanthine-derivative compound of Formula I or a pharmaceutically acceptable salt thereof,



wherein

each of X₁ and X₂ independently represents oxygen or sulfur;

Q represents:

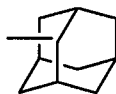


where Y represents a single bond or alkylene having 1 to 4 carbon atoms, n represents 0 or 1;

each of R₁ and R₂ independently represents hydrogen, lower alkyl, allyl, propargyl, or hydroxy-substituted, oxo-substituted or unsubstituted lower alkyl, and R₃ represents hydrogen or lower alkyl, or

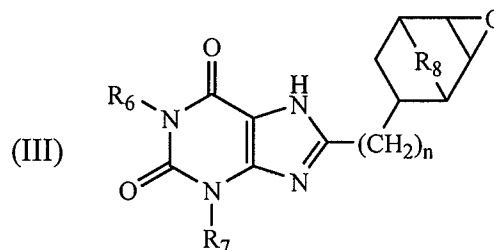
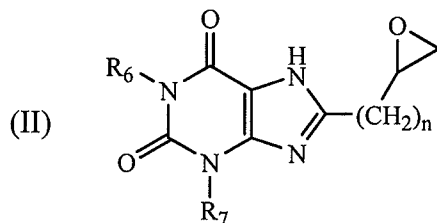
R₄ and R₅ are the same or different and each represent hydrogen or hydroxy, and when both R₄ and R₅ are hydrogen, at least one of R₁ and R₂ is hydroxy-substituted or oxo-substituted lower alkyl,

provided that when Q is



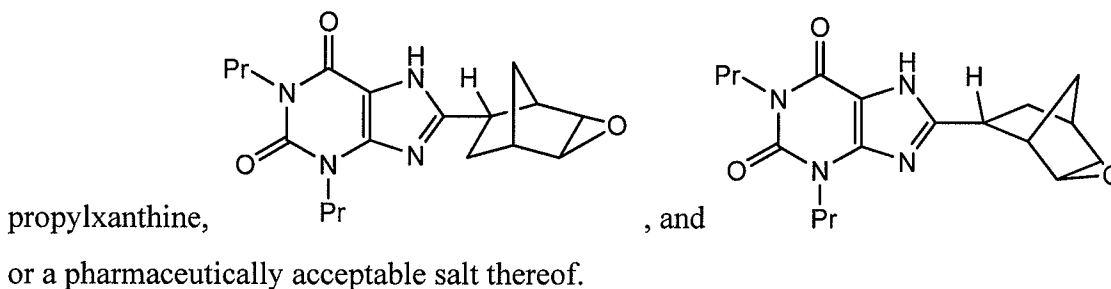
then R₁, R₂ and R₃ are not simultaneously methyl,

or wherein said AA₁RA is a xanthine epoxide-derivative compound of Formula II or Formula III, or a pharmaceutically acceptable salt thereof,



wherein R_6 and R_7 are the same or different, and can be hydrogen or an alkyl group of 1-4 carbons, R_8 is either oxygen or $(CH_2)_{1-4}$, and $n=0-4$.

31. (New) The method of Claim 30, wherein said AA_1RA is selected from the group consisting of 8-(noradamantan-3-yl)-1,3-dipropylxanthine; 1,3-Diallyl-8-(3-noradamantyl)xanthine, 3-allyl-8-(3-noradamantyl)-1-propargylxanthine, 8-(trans-9-hydroxy-3-tricyclo[3.3.1.0^{3,7}]nonyl)-1,3-dipropylxanthine, 8-(cis-9-hydroxy-3-tricyclo[3.3.1.0^{3,7}]nonyl)-1,3-dipropylxanthine, 8-(trans-9-hydroxy-3-tricyclo[3.3.1.0^{3,7}]nonyl)-1-(2-oxopropyl)-3-propylxanthine, 1-(2-hydroxypropyl)-8-(trans-9-hydroxy-3-tricyclo[3.3.1.0^{3,7}]nonyl)-3-



32. (New) The method of Claim 26, wherein said AA_1RA is KW-3902, or a pharmaceutically acceptable salt, ester, amide, or metabolite thereof.

33. (New) The method of Claim 26, wherein said beta blocker is selected from the group consisting of acebutolol hydrochloride, atenolol, betaxolol hydrochloride, bisoprolol fumarate, carteolol hydrochloride, esmolol hydrochloride, metoprolol, metoprolol tartrate, nadolol, penbutolol sulfate, pindolol, propranolol hydrochloride, succinate, and timolol maleate, or a pharmaceutically acceptable salt, prodrug, ester, or amide thereof.

34. (New) The method of Claim 26, wherein said AA_1RA and said beta blocker are administered substantially simultaneously.